

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between uterine contractions before elective caesarean section and transient tachypnoea of the newborn: a retrospective cohort study
AUTHORS	Shinohara, Satoshi; Amemiya, Atsuhito; Takizawa, Motoi

VERSION 1 - REVIEW

REVIEWER	Mariana Santos Felisbino Mendes NURSING SCHOOL, UNIVERSIDADE FEDERAL DE MINIAS GERAIS, BRAZIL
REVIEW RETURNED	27-Aug-2019

GENERAL COMMENTS	<p>COMMENTS TO DE EDITOR AND AUTHORS</p> <p># General comments</p> <p>The manuscript discusses a relevant subject regarding consequences of elective cesareans with evidence supporting negative outcomes for newborns. The manuscript is well-written, concise and comprehensive even though I believe some adjustments are necessary in order to be suitable for publication. The main adjustment is to align data analysis and results according to the study rationale which on my understanding was to assess the association of a main exposure (uterine contractions) with a neonatal outcome transient tachypnoea of the newborn (TTN), which is clear in the title, objective, introduction and conclusion.</p> <p># Introduction</p> <p>1) In the second paragraph there is a sentence which needs furthermore clarification: "The elective caesarean section rate is expected to continue to increase due to increased maternal age,[16] multiple gestations after fertility treatment[17] and physician and maternal concern about the risks of vaginal birth.[18]"</p> <p>This sentence lead to believe authors agree with these "causes" of C-section which are not evidence-based. What are the risks of vaginal birth that physicians and mothers may be concerned?</p> <p>2) In the sentence in page 4-5 lines 58-6 when writing regarding the association, exposure must come first.</p> <p># Methods</p> <p>Since there was a waived informed consent authors may state the procedures to guarantee patients identity and information safety. In Data collection subsection in the second paragraph when authors report that women were grouped would be more</p>
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	<p>appropriate to state the main exposure to be tested. At the end of this same paragraph the TTN should be clearly stated as the outcome of interest in the study.</p> <p>The Statistical analysis subsection requires a larger review because the strategy described in the section is not aligned with the study objective and rationale. There is one exposure to be tested including adjustment for confounders and not several factors associated with TTN. This is confusing.</p> <p># Results</p> <p>1) The first paragraph of this section describes methods aspects and information, thus it must be placed in the methods section, except for the phrase "...mean age, 32.8±5.1; nulliparous, 124 [26.7 %]". Could you describe more the studied population?</p> <p>2) Table 1 p-value column must state which test was used to evaluate the differences, for instance which test was used for means and which was used for proportions?</p> <p>3) Table 2 information and statistics do not support an association, thus the following sentence must be carefully reviewed "The absence of uterine contractions was significantly associated with TTN (Table 2), and the prevalence of TTN was significantly higher in patients without uterine contractions than in those with uterine contractions (14.0 % vs 7.3 %, p=0.02)." Moreover, the test performed (a p value was presented) was not identify and is quite not clear. The denominator of this table in the second column was also not very clear, would it be total number of women with (o, 1, 2, etc) number of contractions?</p> <p>4) As stated in methods reporting results for table 3 must be revised and rewritten according to the main objective of the study.</p> <p># Discussion</p> <p>There are results in this section not previously presented.</p> <p>The following sentence is of great concern: "Antepartum CTG can be routinely performed before elective caesarean section without additional cost to easily and objectively determine the presence or absence of uterine contractions. As TTN is difficult to prevent, obstetricians, paediatricians and other medical professionals involved in an elective caesarean section should be aware of the risk factors of this complication and prepared to administer treatment".</p> <p>Why establish a test which might implicate in continuous monitoring, equipment, and health workers, and so on, instead of discuss the risks of an elective cesarean? C section as elective is not recommended and can implicate in more interventions.</p> <p>In Limitations is not clear how the unmeasured confounders could have affected the study results.</p>
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REVIEWER	Masahiko Nakata Toho University, Japan
REVIEW RETURNED	29-Sep-2019

GENERAL COMMENTS	<p>This manuscript addresses an important issue in the etiology of transient tachypnea of the newborn after elective cesarean section.</p> <p>Although this is well written and illustrated paper, the number of cases is too short to conclude.</p>
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REVIEWER	Behnaz Basiri Hamadan University of Medical Science Iran- Hamadan
REVIEW RETURNED	10-Oct-2019

GENERAL COMMENTS	<p>Dear authors</p> <p>As a neonatologist ,your raticle was very interesting for me.it seems considering of uterine contracture as a determinent of TTN , is a new idea.</p> <p>Although TTN is self limited and benign state in newborn but according to many of infants admitted to NICU for TTN , any more informations about TTN , its pathophysiology and treatment, can help to reducing hospitalization of these newborns.</p> <p>1-Would you please explain about CTG , how do it, what is your device?</p> <p>2- who did make the diagnosis of TTN, and when ?</p> <p>3-Were all of patatients with TTN admitted in NICU?</p>
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VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1

Comment 1

In the second paragraph there is a sentence which needs furthermore clarification:

“The elective caesarean section rate is expected to continue to increase due to increased maternal age,[16] multiple gestations after fertility treatment[17] and physician and maternal concern about the risks of vaginal birth.[18]”

This sentence lead to believe authors agree with these “causes” of C-section which are not evidence-based. What are the risks of vaginal birth that physicians and mothers may be concerned?

Response 1

Thank you for your comment. After reviewing the literature, we changed “physician and maternal concern about the risks of vaginal birth” to “maternal request.”

Comment 2

In the sentence in page 4-5 lines 58-6 when writing regarding the association, exposure must come first.

Response 2

Thank you for your comment. We revised changed “between TTN and the presence of uterine contractions before caesarean section alone” to “between the presence of uterine contractions before caesarean section alone and TTN.”

Comment 3

Since there was a waived informed consent authors may state the procedures to guarantee patients identity and information safety.

Response 3

Thank you for your comment. We added “However, patients were provided the opportunity to refuse the usage of their data through the hospital’s website” in the Study Design subsection.

Comment 4

In Data collection subsection in the second paragraph when authors report that women were grouped would be more appropriate to state the main exposure to be tested. At the end of this same paragraph the TTN should be clearly stated as the outcome of interest in the study.

Response 4

Thank you for your comment. We added “which was the outcome of interest in this study” in the Data Collection subsection.

Comment 5

The Statistical analysis subsection requires a larger review because the strategy described in the section is not aligned with the study objective and rationale. There is one exposure to be tested including adjustment for confounders and not several factors associated with TTN. This is confusing.

Response 5

Thank you for your comment. We added “The logistic regression models were adjusted by uterine contraction, GDM, SGA infants, infant sex and gestational age at delivery” in the Statistical Analyses subsection.

Comment 6

The first paragraph of this section describes methods aspects and information, thus it must be placed in the methods section, except for the phrase “...mean age, 32.8±5.1; nulliparous, 124 [26.7 %]”. Could you describe more the studied population?

Response 6

Thank you for your comment. We removed “During the study period, 523 women underwent elective caesarean section. After excluding 59 patients (missing data, n=12; twin pregnancy, n=38; neonatal asphyxia, n=2; general anaesthesia, n=1; elective caesarean section before term delivery, n=6)” and “Cases of neonatal asphyxia were excluded because this diagnosis was statistically underrepresented in our study sample” from the Results section and added them to the Methods section. Moreover, we added “A total of 464 women were considered eligible for inclusion in this study. The mean maternal age was 32.8±5.1 years, and the mean maternal pre-pregnancy BMI was 21.7±3.9 kg/m², with 124 (26.7%) nulliparous women, 234 male infants (50.4%), 30 GDM women (6.5%), and 34 (7.3%) SGA infants.”

Comment 7

Table 1 p-value column must state which test was used to evaluate the differences, for instance which test was used for means and which was used for proportions?

Response 7

Thank you for your comment. We added “The Mann-Whitney U test was used to analyse continuous variables such as maternal age, and the chi-square test (or Fisher's exact test when the expected frequency was <5) was used for categorical variables such as incidence of obstetric complications” in the Statistical Analyses subsection and footnote.

Comment 8

Table 2 information and statistics do not support an association, thus the following sentence must be carefully reviewed “The absence of uterine contractions was significantly associated with TTN (Table 2), and the prevalence of TTN was significantly higher in patients without uterine contractions than in those with uterine contractions (14.0 % vs 7.3 %, p=0.02).” Moreover, the test performed (a p value was presented) was not identify and is quite not clear.

Response 8

Thank you for your comment. We revised “The absence of uterine contractions was significantly associated with TTN (Table 2)” to “TTN occurred more frequently in women without uterine contractions (Table 2).” Moreover, we added “(Table 1)” after “the prevalence of TTN was significantly higher in patients without uterine contractions than in those with uterine contractions (14.0% vs 7.3%, $p=0.02$).”

Comment 9

The denominator of this table in the second column was also not very clear, would it be total number of women with (0, 1, 2, etc) number of contractions?

Response 9

Thank you for your comment. We revised the column head as “Prevalence of TTN*” added “*Values are presented as the number of TTN per number of women stratified according to the number of uterine contractions (percentage)” As a footnote in Table 2.

Comment 10

As stated in methods reporting results for table 3 must be revised and rewritten according to the main objective of the study.

Response 10

Thank you for your comment. However, GDM, SGA infants, infant sex and gestational age at delivery were included in Table 3 as they are potential confounding factors of TTN, according to previous studies,¹⁻³ and uterine contraction was the main exposure in this study. Therefore, we did not change Table 3.

REFERENCES

- 1, Tutdibi E, Gries K, Bücheler M, et al. Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. *Pediatrics* 2010;125:e577–83.
- 2, Dani C, Reali MF, Bertini G, et al. Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Italian Group of Neonatal Pneumology. *Eur Respir J* 1999;14:155–9.
- 3, Persson B, Hanson U. Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care* 1998;21 Suppl 2:B79–84.

Comment 11

The following sentence is of great concern: “Antepartum CTG can be routinely performed before elective caesarean section without additional cost to easily and objectively determine the presence or absence of uterine contractions. As TTN is difficult to prevent, obstetricians, paediatricians and other medical professionals involved in an elective caesarean section should be aware of the risk factors of this complication and prepared to administer treatment”.

Why establish a test which might implicate in continuous monitoring, equipment, and health workers, and so on, instead of discuss the risks of an elective cesarean? C section as elective is not recommended and can implicate in more interventions.

Response 11

Thank you for your comment. Recently, in Japan, relatively few institutions allow vaginal birth after caesarean (VBAC), as they are concerned about uterine rupture. A previous study reported that approximately 30% institutions allowed planned vaginal birth as an option after CS.¹ Therefore, especially in Japan, it is important to examine the relationship between TTN and elective caesarean section. We added “This is important because, recently, in Japan, relatively few institutions allow vaginal birth after caesarean section, as they are concerned about uterine rupture, with only

approximately 30% of institutions allowing planned vaginal birth as an option after caesarean section.[28]"

Comment 12

In Limitations is not clear how the unmeasured confounders could have affected the study results.

Response 12

Thank you for your comment. We deleted "which may have affected the results of our study." and added "and there is the possibility that unmeasured confounders may be associated with TTN in this study" in the Discussion section.

RESPONSE TO REVIEWER 2

Comment 1

This manuscript addresses an important issue in the etiology of transient tachypnea of the newborn after elective cesarean section.

Although this is well written and illustrated paper, the number of cases is too short to conclude.

Response 1

Thank you for your feedback. We agree that the number of cases is too small to base a conclusion on. However, it is difficult to obtain a high number of patients in this study. Therefore, we added "although studies with larger sample size are required" in the Conclusion section.

RESPONSE TO REVIEWER 3

Comment 1

Would you please explain about CTG, how do it, what is your device?

Response 1

Thank you for your comment. We added "CTG, which records foetal heart rate and uterine contraction, is typically used to assess foetal well-being. In this study, CTG data were recorded using an actocardiograph (Toitu MT-516GE; Tofa Medical Inc., Malvern, PA, USA)" into the Data Collection subsection.

Comment 2

who did make the diagnosis of TTN, and when ?

Response 2

Thank you for your comment. We added "A neonatologist diagnosed TTN based on the above diagnostic criteria in the first few hours after a baby was born" in the Data Collection subsection.

Comment 3

Were all of patients with TTN admitted in NICU?

Response 3

Thank you for your comment. We added "Moreover, when the neonatologist diagnosed TTN, all infants were treated in the neonatal intensive care unit" in the Data Collection subsection.

VERSION 2 – REVIEW

REVIEWER	Masahiko Nakata Toho University Graduate School of Medicine, Japan
REVIEW RETURNED	24-Oct-2019

GENERAL COMMENTS	<p>This manuscript was well written and focused on the important issue to predict transient tachypnea of the newborn in terms of maternal condition before delivery.</p> <p>The authors revised and responded well as the reviewers comments.</p> <p>Although this study is a single center study and the number of cases is small, this manuscript provides an important information that the absence of uterine contraction before cesarean section is one of the risk factor for TTN.</p>
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REVIEWER	Behnaz Basiri Hamadan university of Medical Science Islamic Republic of Iran
REVIEW RETURNED	07-Nov-2019

GENERAL COMMENTS	<p>Dear authors</p> <p>Thank you for correcting the article.</p>
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